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Vroomen, L.G.P.H.

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CHAPTER 9.3

Added Value of CT-Guided Percutaneous Irreversible Electroporation to FOLFIRINOX Chemotherapy in Locally Advanced Pancreatic Cancer: a Post Hoc Comparison

Laurien GPH Vroomen
Eran van Veldhuisen
Alette H Ruarus
Tych C Derksen
Otto R Busch
Marcus C de Jong
Geert Kazemier
Robbert S Puijk
Natasha Sorgedrager
Jantien A Vogel
Hester J Scheffer
Krijn P van Lienden
Johanna W Wilmink
Marc G Besselink
Martijn R Meijerink

Submitted

ABSTRACT

Background: Irreversible electroporation (IRE) is increasingly used in patients with locally advanced pancreatic cancer (LAPC) after FOLFIRINOX. Comparative studies studying the added value of IRE over chemotherapy alone are, however, lacking. We aimed to compare survival after treatment with CT-guided percutaneous IRE and FOLFIRINOX versus FOLFIRINOX alone in patients with LAPC.

Methods: A post-hoc comparison of data from a prospective study cohort (IRE-FOLFIRINOX; PANFIRE trial; NCT01939665) with a matched retrospective FOLFIRINOX-only cohort was performed. All patients received a minimum 3 cycles of FOLFIRINOX for LAPC, had hereafter non-resectable disease but were eligible for CT-guided percutaneous IRE. Endpoints included overall survival (OS), local- and distant progression-free survival (LPFS/DPFS), and time to any progression (TTP). Sensitivity analyses were performed by excluding patients who received >8 cycles of FOLFIRINOX pre-IRE and tumors >6cm in the FOLFIRINOX-only group.

Results: Overall, 103 patients were diagnosed with LAPC of which 52 patients met the eligibility criteria, of whom 30 received percutaneous IRE-FOLFIRINOX and 22 FOLFIRINOX-only. Median OS was 17.0 months (IQR 11.8–19.4) in the IRE-FOLFIRINOX group *versus* 12.4 months (IQR 10.1–19.8) for FOLFIRINOX-only (p=0.038). After sensitivity analyses, median OS was 17.2 months (IQR 10.7–18.9) versus 12.4 months (IQR 10.7–18.9; p=0.05). Median TTP was superior in the IRE-FOLFIRINOX group; 14.2 months (IQR 9.9–5.3) versus 5.2 months (IQR 3.0–10.0; p=0.0001).

Conclusion: In patients with LAPC after induction FOLFIRINOX chemotherapy, CT-guided percutaneous IRE may improve OS and TTP. This study can facilitate the design of randomized-controlled trials which should confirm the benefit of IRE.

INTRODUCTION

Pancreatic cancer remains a disease with a dismal prognosis.[1] Surgical resection in combination with chemotherapy provides the best overall survival but is only feasible in 10-20% of patients.[2] The remaining 80% of patients either present with disseminated disease or locally advanced pancreatic cancer (LAPC)[3], characterized by local tumor involvement with vital structures rendering these patients non-resectable.[4]

Patients with metastatic disease and patients with LAPC are preferably treated with systemic chemotherapy[4], which for decades consisted of gemcitabine-based chemotherapy.[5] The recent implementation of FOLFIRINOX (combination of leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin) has resulted in improved survival of metastatic pancreatic cancer.[6] Extrapolating these results, many centers now use FOLFIRINOX as standard of care for patients with LAPC.[3] Besides a survival benefit, FOLFIRINOX has the ability to downstage unresectable disease to curative intent surgery in approximately 10-30% of patients.[7, 8]

However, despite the downstaging effects of FOLFIRINOX, the largest proportion of patients with LAPC will remain unresectable after 2-4 months chemotherapy. Several local ablative therapies, including irreversible electroporation (IRE), have been investigated as new treatment options for LAPC.[9] When combined with systemic chemotherapy, IRE may hold the potential of a survival benefit with relatively minor morbidity and good quality of life.[9, 10] Median overall survival following IRE for LAPC is reported up to 27 months following IRE and 30 months from diagnosis.[11] However, randomized-controlled trials comparing chemotherapy with-and without IRE are lacking. As a result, the true benefit of IRE in addition to systemic chemotherapy is unclear. In order to determine the added value of IRE we therefore compared the survival of patients treated with both FOLFIRINOX and CT-guided percutaneous IRE with matched patients treated with FOLFIRINOX only.

METHODS

Patients

Post-hoc analysis of data from the prospective percutaneous IRE study cohort (PANFIRE study of the Amsterdam UMC; registered at *clinicaltrials.gov* [identification number NCT01939665]) and the prospective and retrospective FOLFIRINOX cohorts (Amsterdam UMC, location AMC) was conducted.[12-14] Included were patients with pathology-proven LAPC according to the National Comprehensive Cancer Network (NCCN) criteria[15] after treatment with a minimum of 3 cycles of FOLFIRINOX. The following baseline characteristics were collected: age, sex, WHO performance and data on treatment and oncologic outcomes. Results obtained from patients treated with induction FOLFIRINOX chemotherapy followed by IRE (experimental group) were compared to matched patients treated with FOLFIRINOX only (control group). Routine follow-up of patients consisted of three-monthly CT-scans.

FOLFIRINOX plus IRE group

Patients in whom IRE was considered technically feasible, without ventricular arrhythmias and no combined stenosis of the hepatic artery and portal vein >70% were eligible for percutaneous IRE.

The IRE procedures were performed under general anaesthesia using CT-guidance and ECG-synchronization. Depending on tumor size and shape 3 - 8 electrodes were placed, with an active tip length of 1.5 - 2.0 cm and a maximum inter-electrode distance of 2.5 cm. IRE treatment was initiated with 10 test pulses of 1,500 volts per centimetre (V/cm), with a pulse duration of 90 μs; to reach a current of 20-40 ampere (A), voltage adjustments were allowed. Subsequently, 90 treatment pulses were delivered, and if necessary, a pullback of the electrodes was performed and the procedure was repeated to treat the more superficial part of the tumor.

FOLFIRINOX-only group

Patients who were treated with FOLFIRINOX only were post-hoc assessed for percutaneous IRE eligibility by two experienced interventional radiologists who had each performed >25 and >200 percutaneous IRE procedures, respectively. Only patients considered suitable for percutaneous IRE after a minimum 3 cycles

of FOLFIRINOX were included in the present analysis. Patients with (borderline) resectable disease after induction FOLFIRINOX chemotherapy were excluded from the present study as they would generally undergo a resection (and are therefore no candidates for percutaneous IRE).

FOLFIRINOX was administered to patients in good clinical condition (i.e. World Health Organization [WHO] performance score 0-1) and consisted of two-weekly cycles of oxaliplatin at a dose of 85 mg/m2, given as a 2-hour intravenous (i.v.) infusion, immediately followed by leucovorin at a dose of 400 mg/m2, given as a 2-hour i.v. infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg/m2, given as a 90-minute i.v. infusion. This treatment was immediately followed by fluorouracil at a dose of 400 mg/m2, administered by i.v. bolus, followed by a continuous i.v. infusion of 2400 mg/m2 over a 46-hour period.[6] FOLFIRINOX dose reductions were allowed in case of toxicity or at patients' request.

Definitions

Resectability was defined according to the National Comprehensive Cancer Network (NCCN) criteria.[15] Restaging of disease was performed according to the Response Evaluation Criteria in Solid Tumours (RECIST).[16] Local progression free survival was defined as the time between start of chemotherapy and unequivocal local progression (i.e. >20% increase in tumor diameter) or death due to any cause. Distant progression free survival was defined as the time between start of chemotherapy and unequivocal recurrence distant to the treatment site or death due to any cause. Time to progression (TTP) was defined as the time between start of chemotherapy and any radiologic progression (i.e. local and/or distant progression), with death without objectified disease recurrence being censored. Overall survival was defined as the time between radiologic diagnosis and death due to any cause.

Statistical analysis

Normally distributed data are presented as mean and standard deviation (SD), non-normally distributed data as median and interquartile range (IQR). Patients alive at last follow-up were censored. Stratified Kaplan-Meier curves were used to compare survival between the IRE-FOLFIRINOX group versus FOLFIRINOX-only using the Breslow test.

Additional sensitivity analyses were performed, aimed at reducing the risk of selection and immortal time bias, excluding: (1) patients in the FOLFIRINOX-only group with a tumor diameter >6 cm; (2) patients in the IRE group who received >8 cycles of FOLFIRINOX prior to the ablation. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0. (Armonk, NY: IBM Corp). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 103 patients diagnosed with LAPC between November 29th, 2010 and August 31st, 2017 were identified. Of these, 52 patients met all eligibility criteria, of whom 30 received percutaneous IRE preceded by induction FOLFIRINOX chemotherapy and 22 were treated with FOLFIRINOX-only, see Figure 1. The baseline characteristics of these patients are shown in Table 1.

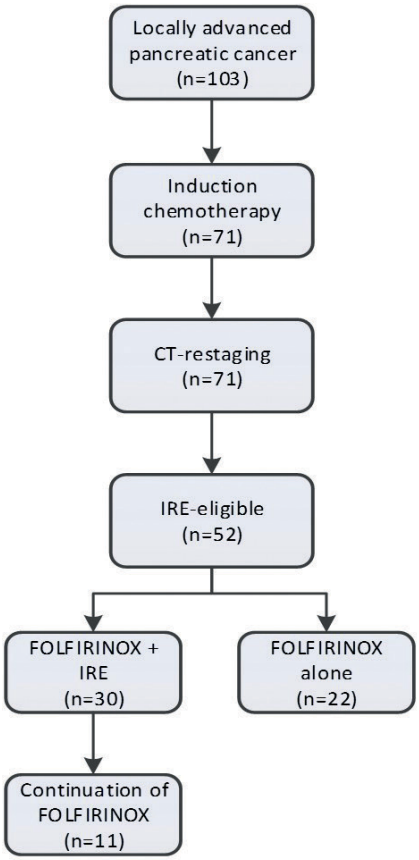

Figure 1. Flow-chart of patient follow-up. IRE: Irreversible Electroporation; CT: Computed Tomography

Table 1: Baseline characteristics

Baseline characteristics	IRE-FOLFIRINOX (n=30)	FOLFIRINOX-only (n=22)
Male (percent)	18 (60)	14 (64)
Age, year, mean (sd)	62 (9)	59 (9)
WHO-score, no. (percent)	17 (53)	12 (55)
0	10 (31)	8 (36)
1	3 (16)	2 (9)
Unknown		
Tumor variables		
Size, mm, mean (sd)	38 (7)	53 (19)
Pathologic lymph nodes, no. (per cent)	2 (7)	5 (23)
Biliary drainage prior to treatment, no. (percent)	10 (33)	13 (59)
Previous surgery, no. (percent)	0 (0)	3 (14)
Exploration	1 (3)	0 (0)
Diagnostic laparoscopy	30 (100)	18 (82)
No previous surgery		
Median total number of cycles FOLFIRINOX (IQR)	6 (5 – 8)	7 (5 –8)
Radiation therapy, no (percent)	2 (7)	7 (32)

SD: Standard Deviation; WHO: World Health Organization; CI: Confidence Interval; PDAC: Pancreatic Ductal Adenocarcinoma.

IRE-FOLFIRINOX group

In the IRE-FOLFIRINOX group, 14 patients were male (47%) and the mean age was 62 ± 9 years. Fifteen patients had a WHO performance score of 0, the remaining patients had WHO 1 (n=11, 50%) or unknown performance status (n=6). Two patients had received prior radiotherapy. Following induction FOLFIRINOX chemotherapy (median 6 cycles (IQR 5-8), one patient had RECIST partial response (3%), three had progression (10%) of disease and the remaining patients had RECIST stable disease (87%). One patient underwent a staging laparoscopy prior to IRE. After the IRE procedures, 11 patients received adjuvant chemotherapy (42%; median 4 [IQR 2-6]).

FOLFIRINOX-only group

In the FOLFIRINOX-only group, 14 patients were male (64%) with mean age 59 ± 9 years. Most patients had a WHO score of 0 (n=12, 55%). Three patients underwent

explorative laparotomy (14%) prior to FOLFIRINOX administration, but did not undergo resection. Patients received a median 7 cycles of FOLFIRINOX (IQR 5 - 8). Seven patients (32%) had received radiotherapy. Of these, one patient received radiotherapy due to a bleeding duodenal ulcer, four patients were treated for pain relief and two patients received stereotactic radiotherapy. Following FOLFIRINOX chemotherapy, partial response of disease according to the RECIST-criteria was seen in 1 patient (4%). The remaining patients had stable disease (n=16, 67%) or progression (n=5, 21%) respectively.

Survival

Median OS was 17.0 months (IQR 11.8 – 19.4) in the IRE-FOLFIRINOX group versus 12.4 months (IQR 10.1 – 19.8) in the FOLFIRINOX-only group, p=0.038. Median time to progression was 14.2 months (IQR 9.9 – 15.3) compared to 5.2 months (IQR 3.0 – 10.0) for the IRE-FOLFIRINOX and FOLFIRINOX-only group (p<0.001), respectively (Figure 2). A median local progression-free survival of 17.1 months (IQR 10.4 – 17.1) versus 9.9 months (IQR 3.0 – 10.0) was observed for the IRE-FOLFIRINOX versus FOLFIRINOX-only group (p=0.013). Median distant progression-free survival was 16.0 months (IQR 10.4. – 15.3) for IRE-FOLFIRINOX group vs 11.9 months (IQR 3.5 – 10.0) for the FOLFIRINOX-only group (p=0.001).

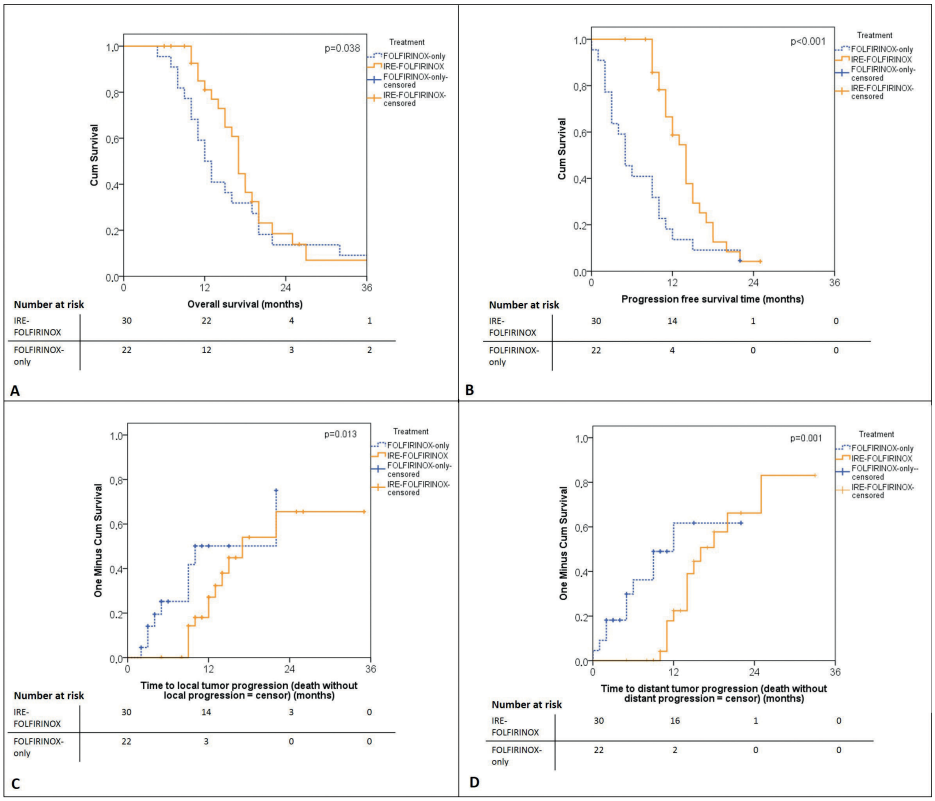

Figure 2. Overall survival (A), time to progression (B), local (C)- and distant progression-free survival (D) of patients with LAPC after at least 3 cycles of FOLFIRINOX, treated with or without IRE.

Sensitivity analysis

Forty-one patients were included in the sensitivity analysis. Seven and four patients were excluded from the IRE-FOLFIRINOX group (>8 cycles FOLFIRINOX) and the FOLFIRINOX-only group (tumor diameter >6cm), respectively. Hereafter, median overall survival and time to progression remained favorable for the group treated with IRE-FOLFIRINOX (Table 2. The survival outcomes are depicted in Kaplan-Meier curves, see Figures 2 and 3.

Table 2. Median time to progression, overall-and local-progression free survival of IRE-FOLFIRINOX versus FOLFIRINOX-only.

	IRE-FOLFIRINOX (n=23)	***FOLFIRINOX only (n=18)***	***p value***
Median overall survival	17.2 (IQR 10.7 – 18.9)	12.4 (IQR 8.8 – 19.8)	0.05
Median time to progression	13.1 (IQR 9.5 – 15.3)	4.9 (IQR 3.0 – 8.7)	<0.001
Median local progression-free survival	15.2 (IQR 11.8 – 15.3)	8.7 (IQR 3.4 – 8.7)	0.003
Median distant progression-free survival	19.5 (IQR 11.8 – 17.2)	8.7 (IQR 3.0 – 8.7)	<0.001

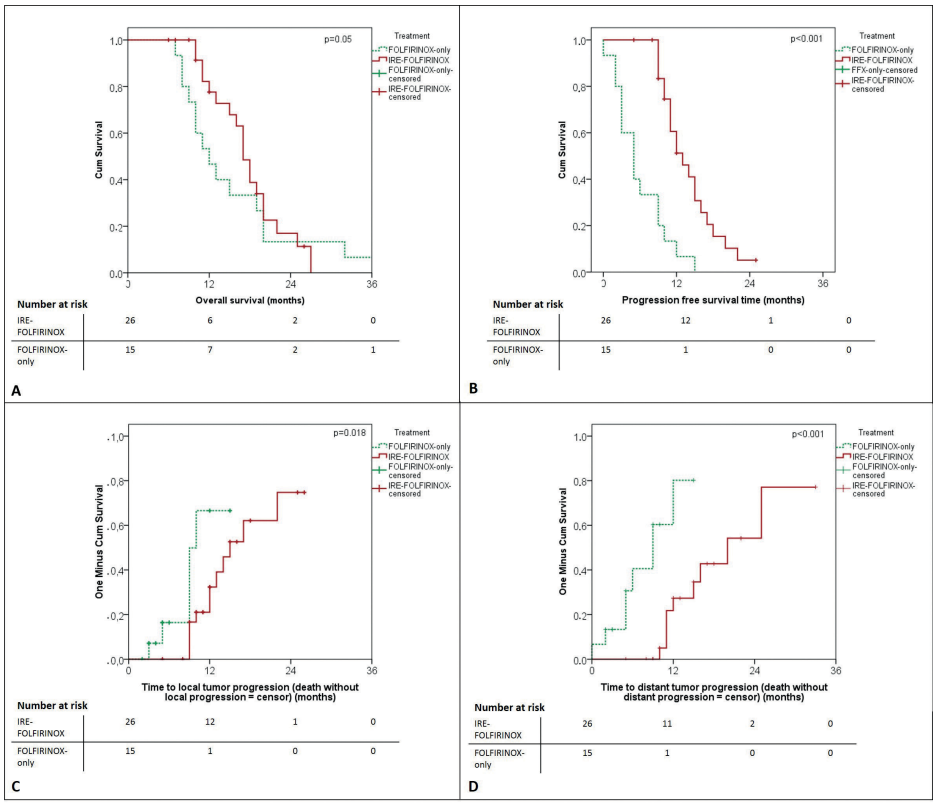

Figure 3. Overall survival (A), time to progression (B), local (C)- and distant progression-free survival (D) of patients with LAPC after at least 3 cycles of FOLFIRINOX, treated with or without IRE after sensitivity analyses.

DISCUSSION

The present post-hoc matched study suggests that in patients with LAPC after systemic FOLFIRINOX chemotherapy, CT-guided percutaneous IRE could provide a survival benefit. In the present cohort, FOLFIRINOX plus IRE demonstrated a 4.6 months gain in median overall survival and a 9.0 months gain in median time to progression over FOLFIRINOX-only.

Previous studies on percutaneous and open IRE after induction chemotherapy have suggested a possible survival benefit over systemic chemotherapy alone.[9, 13, 17] However, due to the heterogeneity in patient population and administered chemotherapeutic (and/or radiotherapeutic) regimens, there is a large variety in the reported clinical outcomes. As a result, median OS for systemic treatment combined with IRE ranges 15.3 to 30.0 months between studies.[9, 11, 14] This makes it impossible to compare outcomes with retrospective FOLFIRINOX-only cohorts that range from 10.0 to 32.7 months.[8] A propensity-matched study by Martin et al. compared patients receiving IRE after induction chemotherapy with a retrospective cohort of patients receiving chemotherapy alone. The authors reported a significant improvement in overall survival from 13 to 20 months (p=0.003), LPFS from 6 to 14 months (p=0.01), and DPFS from 9 to 15 months (p=0.02 in favor of the patients receiving IRE plus chemotherapy. However, only a small proportion of the included patients received FOLFIRINOX, making it difficult to translate these results to current practice.[18]

Prolonging life expectancy without jeopardizing quality of life for patients with LAPC is crucial as the current survival remains poor.[14] The combination of systemic chemotherapy and cytoreductive ablation using IRE may prove synergistic for several reasons.[9] Induction systemic chemotherapy may not only downstage a subset of patients to curative-intent surgery, it may also help to identify patients with biologically unfavorable tumors with rapid progression who will unlikely benefit from local ablative therapy. It is quintessential to avoid invasive procedures that may compromise quality of life in this subgroup with such a poor prognosis.[19] There is a growing body of literature suggesting that FOLFIRINOX may be most effective in treating occult micro-metastatic disease.[20, 21] Moreover, the authors believe that performing upfront IRE could preclude a sub-set of patients from receiving adjuvant chemotherapy in the case of severe IRE-related complications.[22]

In the era of FOLFIRINOX chemotherapy, resection rates and survival of LAPC following induction chemotherapy are improving. Previous studies have suggested a median overall survival of 34 months following resection of LAPC after neoadjuvant FOLFIRINOX[8, 14, 23], with resection rates varying between 11-60%.[14, 24] However, a large proportion of LAPC patients will remain unresectable despite induction chemotherapy treatment, and effective local ablation combined with systemic therapy may therefore prove a valuable approach in this setting.

The results of this study must be interpreted in the light of several limitations. First, this was a non-randomized study, which compared both retro- and prospectively collected data. This could have caused information bias. However, since patients were matched and survival was the primary endpoint this bias could have been of limited influence. Second, even after excluding tumors larger than 6 cm in the FOLFIRINOX-only group, the mean maximum tumor diameter remained significantly larger in the FOLFIRINOX-only group. Although there is currently no evidence to suggest that larger tumors are associated with a worse prognosis, this finding could have led to residual confounding. Nonetheless, in the sensitivity analysis, excluding all tumors larger than 6 cm, we found that the differences in overall and progression free survival were still in favor of IRE-FOLFIRINOX. Despite matching, there are no guarantees that residual confounders exist. One of these confounders may also be allocation bias, which may reflect the difference in DPFS between IRE-FOLFIRINOX and FOLFIRINOX-only. It could be hypothesized that the patients undergoing IRE-FOLFIRINOX were able to receive IRE because they did not develop metastases in the time between induction treatment and percutaneous IRE. Second, the median 6 cycles of FOLFIRINOX (3 months) prior to IRE may be considered as shortcoming in some centers. Although we currently have no evidence to support the superiority of a longer induction treatment, this could explain the relatively low overall survival of the IRE-FOLFIRINOX group compared with current literature.[10, 11] Finally, this study has relatively small sample-size. Ideally, future multicenter randomized-controlled trials should establish the true benefit of IRE to FOLFIRINOX chemotherapy in patients with LAPC.

In conclusion, in patients with LAPC after induction FOLFIRINOX chemotherapy, CT-guided percutaneous IRE seems to improve overall, disease-free and progression-free survival. This study may facilitate the design of randomized-

controlled trials which should confirm the benefit of IRE-FOLFIRINOX over FOLFIRINOX-only.

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